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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/017,715	02/03/98	JI H	1488.0810003

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EXAMINER	
CANELLA,K	
ART UNIT	**PAPER NUMBER**
1642	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/017,715	Ji et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *16-79* is/are pending in the applica

4a) Of the above, claim(s) *79* is/are withdrawn from considera

5) ☒ Claim(s) *16-47, 50, 51, 53, 57-70, and 78* is/are allowed.

6) ☒ Claim(s) *48, 49, 52, 54-56, and 71-77* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Response to Amendment

1. Claim 71 has been amended. Claims 16-79 are pending. Claim 79, drawn to a non-elected invention, remains withdrawn from consideration. Claims 16-78 are under consideration.

2. Applicant insists that the partial waiver requirements of 37 C.F.R. 1.141 is to be applied to the instant application entitling applicant to a search of ten sequences, even though the sequences in question are full length cDNAs transcribed from distinct genes. This is not found persuasive and for the reasons set forth in Paper No. 17, the restriction requirement is deemed to be proper and is adhered to. The requirement is therefore made FINAL.

3. Claims 48, 49, 52, 54-56 and 71-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides encoding amino acids 1-127 of SEQ ID NO:2, polynucleotides encoding amino acids 2-127 of SEQ ID NO:2, the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 97856, isolated polynucleotides comprising nucleotides 15-392 of SEQ ID NO:1, polynucleotides comprising nucleotides 12-392 of SEQ ID NO:1, polynucleotides comprising 50, 100, 250 contiguous nucleotides of the coding region of SEQ ID NO:1 or the complement thereof, vectors and host cells comprising 50, 100, 250 contiguous nucleotides of the coding region of SEQ ID NO:1, does not reasonably provide enablement for polynucleotides comprising nucleic acid 95% or more identical to a nucleic acid encoding amino acids 1-127 of SEQ ID NO:2 or amino acids 2-127 of SEQ ID NO:2, polynucleotides encoding an amino acid sequence having one to thirty conservative amino acid substitutions in amino acids 1-127 of SEQ ID NO:2, amino acids 2-127 of SEQ ID NO:2, expression of the peptide encoded by the claimed fragments, or expression of a heterologous polynucleotide beyond what is commonly used in the art for vector replication, such as the expression of beta lactamase for ampicillin resistance, or a pharmaceutical composition

comprising 50 contiguous nucleotides of the coding region of SEQ ID NO:1 or the complement thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

(A)As drawn to the expression of polynucleotides comprising a 50 contiguous nucleotides of the coding region of SEQ ID NO:1.

Claims 48 and 49 are drawn to an isolated polynucleotide comprising 50 contiguous nucleotides of the coding region of SEQ ID NO:1, or the complement thereof, further comprising a heterologous polynucleotide which encodes a heterologous polypeptide. Claims 52 and 54 is drawn to the "operable association" of said 55 contiguous nucleotides, or complement thereof, with a "heterologous regulatory sequence", such as a promoter and a host cell containing said sequences. Claim 55 is drawn to a method of producing a polypeptide comprising the recombinant expression of said 55 contiguous nucleotides, or complement thereof. The specification states that such isolated molecules, particularly DNA molecules are useful as probes for gene mapping by in situ hybridization with chromosomes, and for detecting the BCSG1 gene in human samples by Northern analysis and as such could be maintained and replicated in plasmid form. The specification does not provide any guidance as to the function of these encoded polypeptide fragments or nucleic acids constructs incorporating heterologous regulatory sequences. The specification teaches only polynucleotides comprising nucleic acids which encode fragments of SEQ ID NO:2 from amino acids 94-107 and amino acids 120-127 as antigenic regions of the BCSG1 protein. Applicant has provided Exhibit A as part of Paper No. 18 linking the expression of BCSG1 polynucleotides with stage specific breast cancer. However, there are no teachings in the specification regarding a utility for polynucleotides comprising 50, 100 or 250 contiguous nucleotides of SEQ ID NO:1 beyond use as a hybridization probe. No guidance or examples are given in the specification regarding the specific function activity of polypeptides encoded by these fragments of SEQ ID NO:1, and furthermore, no direction has been given in the

specification regarding the criteria for the selection of a fragment to be expressed. The specification fails to provide an enabling disclosure for how one would use such polypeptide fragments. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art on how to use the broadly claimed species. For the above reasons, undue experimentation would be required to practice the claimed invention.

(B)As drawn to pharmaceutical compositions comprising 50 contiguous nucleotides of the coding region of SEQ ID NO:1 or the complement thereof

Claim 56 is drawn to a composition comprising 50 contiguous nucleotides of the coding region of SEQ ID NO:1 or the complement thereof, and a pharmaceutically acceptable carrier. As such this claim encompasses an anti-sense composition for gene therapy and the specification does not enable a claim drawn to an anti-sense composition comprising a non-specific fragment of the coding region of SEQ ID NO:1. The specification and art of record teach a correlation between the level of BCSG1 expression and stages of breast cancer. The specification does not teach or provide guidance on the administration of an antisense composition directed to BCSG1 expression.

It is recognized in the art that the development of clinically useful antisense strategies for disease therapy is fraught with difficulties, even when the complete nucleic acid sequence for the target protein is known. Antisense nucleic acids, such as antisense cDNA or antisense exons, that are large and highly charged often interact with a wide variety of untargeted cellular components causing undesirable "non-antisense effects" (A.Branch, Hepatology, 1996, Vol. 24, pp. 1517-1529). Antisense nucleic acids must be optimized for use in patients. The published data indicates that only a small percentage of the antisense oligonucleotides which are tested in vitro are actually effective in the reduction of the target mRNA, and that the ability of the anti-sense oligonucleotides to bind to a target mRNA cannot be predicted due to the structure and conformation assumed by individual mRNA specie (Broaddus et al, pg. 122). Further, even if the

specific structure and conformation of a particular mRNA could be adequately predicted as an isolated molecule in a protein-free environment, it would not anticipate the accessible sites for the anti-sense oligonucleotide in vivo, wherein proteins are available to bind to the mRNA thus obscuring the oligonucleotide binding sites and potentially altering the conformation of the target mRNA. Broaddus et al teaches that a highly empirical approach to the testing of candidate anti-sense oligonucleotides is critical for the establishment of an antisense oligonucleotide as a therapeutic agent for the treatment of patients. This requirement has not been met by the instant specification, therefore, one of skill in the art would be forced into undue experimentation without reasonable expectation of success in order to practice the invention as claimed.

(C)As drawn to variant polynucleotides

Claim 71 is drawn to a polynucleotide comprising a nucleic acid which is 95% identical to the nucleic acid encoding amino acids 1 to 127 or 2-127 of SEQ ID NO:2, or the amino acid sequence encoded by the cDNA clone of ATCC Deposit No. 97856. Claim 72 is drawn to a polynucleotide comprising a nucleic acid sequence encoding amino acids 1 to 127 or 2-127 of SEQ ID NO:2, or the amino acid sequence encoded by the cDNA clone of ATCC Deposit No. 97856 with the exception of one to thirty conservative amino acid substitutions. Claim 76 is drawn to an isolated nucleic acid sequence encoding an amino acid sequence which is 95% or more identical to amino acids 1 to 127 or 2-127 of SEQ ID NO:2, or the amino acid sequence encoded by the cDNA clone of ATCC Deposit No. 97856. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims since the specification gives no guidance on or exemplification of how to make/use the variant polynucleotides or the polynucleotides encoding the variant polypeptide as the result of any given amino acid substitution cannot be anticipated. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, as disclosed by Burgess et al (Journal of Cell Biology, 1990, Vol. 111, pp.2129-2138), replacement of a single lysine reside at position 118 of acidic fibroblast growth

factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. (Lazar et al, Molecular and Cellular Biology, 1988, Vol. 8, pp.1247-1252). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Clearly, it could not be predicted that polynucleotide, or a variant, that encodes a protein having thirty amino acid substitutions within SEQ ID NO:2 would even be related to BCSG1 or that a polynucleotide variant of SEQ ID NO:1 will function as an indicator of breast cancer. Applicant argues that it is not necessary to determine which amino acids can be substituted to obtain a protein having BCSG1 activity as all the polynucleotides of the claims are useful as probes to detect breast cancer. This is not found persuasive. The specification provides no objective evidence to support the assertion that a polynucleotide having 95% sequence identity to SEQ ID NO:1, or a polynucleotide encoding an amino acid sequence having 95% identity to SEQ ID NO:2, or a polynucleotide encoding an amino acid sequence having one to thirty conservative substitutions in SEQ ID NO:2 would correlated with stage specific breast cancer. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use variant polynucleotides, or polynucleotides encoding variant polypeptides. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

4. All other rejections and objections as stated in Paper No. 17 are withdrawn.

Conclusion

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Patent Examiner, Group 1642
May 4, 2001

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